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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/682,584	10/09/2003	Sinan Tas	M67.2-11341-US01	9769

490 7590 04/19/2007
VIDAS, ARRETT & STEINKRAUS, P.A.
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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	**PAPER NUMBER**
1614	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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Office Action Summary	**Application No.** 10/682,584	**Applicant(s)** TAS ET AL.
	Examiner James D. Anderson	**Art Unit** 1614

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2007*.
2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 29-35* is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) *1-12 and 29-35* is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.
10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a)☐ All b)☐ Some * c)☐ None of:
1.☐ Certified copies of the priority documents have been received.
2.☐ Certified copies of the priority documents have been received in Application No. _____.
3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed 1/10/2007, have been fully considered and are persuasive in part. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application. In light of the new rejections being applied against the claims, this Office Action is Non-Final.

Status of the Claims

Claims 1-12 and 29-35 are currently pending and are the subject of this Office Action. Claims 1-3 are presently amended and claims 29-35 are newly presented.

Response to Arguments

Applicant's arguments filed 1/10/2007 have been fully considered but they are not persuasive.

Firstly, Applicants argue that the specification provides an adequate written description of "derivatives" of cyclopamine. Applicants assert that the claims are not drawn to the derivatives *per se* and consequently, the cases cited in the Office Action are inapplicable. This argument is not persuasive because while it is true that the claims are not drawn to the derivatives *per se*, the claims require the use of said derivatives. As such, the specification must provide an adequate written description of said derivatives so as to convey that Applicants were in possession of them at the time the application was filed. In this case, there is no indication that Applicants were in possession of any derivatives of cyclopamine. Simply stating that one skilled in the art could screen compounds to find derivatives of cyclopamine in no way demonstrates possession of the compounds. Applicants further argue that the Office is imposing a stricter standard in the present case than is routinely applied to method claims of other applications. This is not persuasive because patents are property, not legal precedent. Each case is examined on its own merit. The fact that some issued patents have the word "derivative" in the claims does not mean that all patent applications have, *a priori*, adequate written description for "derivatives" of compounds being claimed. The Declaration of Dr. Tas (submitted 1/10/2007) and references cited therein has been considered but are not persuasive. The rejection of claims 1-12 (now claims 1-12 and 29-32) under 35 U.S.C. 112, 1st Paragraph (Written Description) is maintained for the reasons of record and reiterated below.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12 and 29-32 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

The claims are drawn to "derivatives" of cyclopamine. The specification teaches that molecules can be derived from cyclopamine or synthesized in such a way that they possess related structural features to exert similar receptor binding properties and biological effects as cyclopamine (page 10, lines 8-10). The specification also discloses that the term "derivative of cyclopamine" is used to refer to such a molecule (page 10, lines 10-11). Such a compound is taught to bind specifically to the same biological target as cyclopamine to cause inhibition of Hh/Smo signaling and the technical effects described in claim 1. The specification does not disclose any particular cyclopamine derivatives as broadly encompassed in the claims.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In the instant case, the only factor present in the claims is a recitation of "derivative" of cyclopamine. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Although drawn to the DNA arts, the findings in *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and *Enzo Biochem, Inc. v. Gen-Probe Inc.* are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in *Lilly*. The court stated that, "[A] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name', of the claimed subject matter sufficient to distinguish it from other materials. " *Lilly* at 1567, 43 USPQ2d at 1405. The court also stated that:

> "[A] generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA' without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is." *Id.* at 1568, 43 USPQ2d at 1406.

The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." *Id.*

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." *Id.*

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The *Enzo* court adopted the standard that "the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Id.* at 1324, 63 USPQ2d at 1613 (emphasis added, bracketed material in original).

While the inventions at issue in *Lilly* and *Enzo* were DNA constructs *per se*, the holdings of those cases are also applicable to claims such as those at issue here (which are drawn to "derivatives" of a known compound). The instant specification may provide an adequate written description of a "derivative" of cyclopamine, per *Lilly*, by structurally describing representative derivatives (*e.g.*, specific compounds), or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per *Enzo*, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not directly describe "derivative[s]" of cyclopamine useful in the claimed invention in a manner that satisfies either the *Lilly* or *Enzo* standards. Although the specification generally describes the function of derivatives of cyclopamine, this does not provide a description of the broadly derivatives of cyclopamine that would satisfy the standard set out in *Enzo* because the specification provides no functional characteristics coupled to structural features (*i.e.*, what specific structural feature of cyclopamine, for example, imparts biological activity). Further, the specification also fails to describe derivatives of cyclopamine by the test set out in *Lilly* because the specification does not describe any particular examples of derivatives of cyclopamine. Therefore it necessarily fails to describe a representative number of such species.

Thus, the specification does not provide an adequate written description of derivatives of cyclopamine that is required to practice the claimed invention. As noted previously, testing to find derivatives is insufficient to provide written description basis for contemplation of chemical formulas for such chemicals.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-6, 8-9, 11-12 and 29-35 are rejected under 35 U.S.C. § 102(e)(2) as being anticipated by Beachy *et al.* (U.S. Patent No. 6,432,970 B2; Issued Aug. 13, 2002; Filed Jun. 4, 1998).

The instant claims recite methods for inducing differentiation and apoptosis of tumor cells that use the Hedgehog/Smoothened signaling for inhibition of differentiation and apoptosis comprising administering a sufficient quantity of cyclopamine to induce differentiation and apoptosis of the tumor cells.

Beachy *et al.* teach methods of inhibiting paracrine and/or autocrine signals produced by a hedgehog protein comprising contacting a cell sensitive to the hedgehog protein with a steroidal alkaloid in a sufficient amount to reduce the sensitivity of the cell to the hedgehog protein (Abstract and col. 4, lines 57-62). The reference thus reasonably anticipates contacting susceptible tumor cells with a steroidal alkaloid. Hedgehog proteins are taught to be essential for patterning a variety of structures in animal embryogenesis and play a role in regulating cell proliferation and specifying cell identity in diverse systems in adults (col. 7, lines 8-12). The invention taught in Beachy *et al.* relates to the discovery that signal transduction pathways dependent on hedgehog proteins can be inhibited by compounds which disrupt the cholesterol modification of hedgehog proteins and/or which inhibit the bioactivity of hedgehog proteins (*id.* at lines 50-54). Suitable steroid alkaloids include cyclopamine (Figure 1 and col. 19, lines 35-42). The reference thus reasonably anticipates administering cyclopamine to a cell to inhibit the bioactivity of hedgehog proteins. The methods of Beachy *et al.* can be effective for both human and animal subjects (col. 8, lines 62-63). The reference thus reasonably anticipates *in vivo* administration. With respect to an "effective amount" of a compound, which reasonably correlates with the instantly claimed "sufficient quantity", Beachy *et al.* teach that an effective amount of, *e.g.*, a hedgehog antagonist, refers to an amount of the antagonist in a preparation which, when applied as part of a desired dosage regimen brings about, *e.g.*, "a change in the rate of cell proliferation and/or the state of differentiation of a cell and/or rate of survival of a cell" according to clinically acceptable standards for the disorder to be treated (col. 9, lines 8-14). The reference thus reasonably anticipates inducing differentiation and apoptosis (rate of survival) by administering a hedgehog antagonist. Similarly, "therapeutically-effective amount" is defined as the amount of a compound which is effective to produce some desired therapeutic effect by inhibiting a hedgehog signaling pathway in at least a sub-population of cells in an animal and thereby blocking the biological consequences of that pathway in the treated cells (col. 45, lines 9-17). This teaching reasonably anticipates inducing differentiation and apoptosis in a cell if the "biological consequence" of hedgehog signaling is inhibition of differentiation and apoptosis. With respect to the treatment of tumors as instantly claimed, Beachy *et al.* contemplate the treatment of carcinomas, including basal cell carcinoma (as recited in instant claim 4) (col. 11, lines 9-14; col. 42, lines 43-49). An exemplary application of the method taught in the reference is a method of "modulating a differentiated state, survival, and/or proliferation of a cell responsive to a hedgehog protein, by contacting the cells with a hedgehog antagonist according to the subject method and as the circumstances may warrant" (col. 29, lines 34-38). The reference thus reasonably anticipates inducing differentiation and apoptosis in tumor cells. In another embodiment, the methods of Beachy *et al.* can be used in the treatment of neoplastic or hyperplastic transformations such as may occur in the central nervous system (col. 33, lines 21-23). Such neoplastic transformations reasonably include tumors. In this case, hedgehog antagonists "can be utilized to cause such transformed cells to become either post-mitotic or apoptotic" (*id.* at lines 24-26). Pharmaceutical compositions wherein the hedgehog antagonists are formulated for administration with biologically acceptable mediums such as water, buffered saline, polyols or suitable mixtures are taught at column 42, lines 57-62). This teaching anticipates instant claims 5-6. Administration routes include oral, parenteral, topical and rectal (col. 43, lines 26-33). Dosage levels vary so as to achieve the desired therapeutic response for a particular patient, composition and mode of administration (col. 43, line 64 to col. 44, line 2). Generally, for intravenous or subcutaneous administration, the dose of the compounds ranges from 0.0001 to 100 mg per kilogram of body weight per day (col. 44, lines 26-29).

The reference thus clearly anticipates administering a steroid alkaloid such as cyclopamine to tumor cells, thereby inducing differentiation and apoptosis.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 7 and 10 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Beachy *et al.* (U.S. Patent No. 6,432,970 B2; Issued Aug. 13, 2002; Filed Jun. 4, 1998) as applied to claims 1-6, 8-9, 11-12 and 29-35 above.

Instant claim 7 recites liposomal forms of cyclopamine. Instant claim 10 recites a controlled release form of cyclopamine.

Beachy *et al.* disclose as discussed *supra*. In summary, the reference teaches pharmaceutical compositions and formulations of steroid alkaloids suitable for administering to humans.

In the absence of a showing of unexpected results commensurate in scope with the claims, the instantly claimed pharmaceutical dosage forms would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. The skilled artisan would have been highly motivated to optimize and modify the dosage forms disclosed in Beachy *et al.* Liposomal and controlled release formulations are well known in the art. As such, it is not unobvious to administer a therapeutic drug in such formulations. Beachy *et al.* disclose numerous pharmaceutically-acceptable carriers that may be used to administer the disclosed steroid alkaloids (col. 45, lines 26-51). As such, it would have been obvious that other carriers, including liposomes and controlled release carriers, could also be used effectively.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson, Ph.D.
Patent Examiner
AU 1614

April 12, 2007

Phyllis Spivack
4/12/07

PHYLLIS SPIVACK
PRIMARY EXAMINER